UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 23 1998

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Hydrolysis study of 1,2-Benzisothiazole-3(2H)-one

From: Akiva D. Abramovitch, Ph.D. Akiva Abramovitch
Senior Scientist

To: Marshall Swindell
PM 33

Dennis Edwards
Branch Chief
Registration Branch I
Antimicrobial Division

Thru: Winston Dang, Ph.D. 7/16/98
Team Leader
Team One
Risk Assessment and Science Support Branch
Antimicrobial Division (7510W)

Norm Cook, Chief 07/23/98
Risk Assessment and Science Support Branch
Antimicrobial Division (7510W)

DP Barcode:241126.

Pesticide Chemical No.:098901

EPA MRID:441821-01

Review Time: 2 days

The registrant did not satisfy the hydrolysis data requirement for the registration of 1,2-benzisothiazol-3(2H)-one since the study as reported did not follow guideline requirements.

The study review cited several major defficiencies:

Some of the major defficiencies relate to lack of sufficient information in the experimental section:

a) The purity of the test material was not specified.

b) It was not specified whether the study was run under sterile conditions to prevent microbial degradation.

c) It was not reported whether precautions were taken to avoid photodegradation with exposure to sunlight.

d) The concentration of the corresponding buffers and how pH was adjusted and monitored during the study period were not specified.

e) The use of traps to acount for all volatiles and a complete material balance was not reported.

The study may be upgraded to acceptable with additional information. For exmple, the registrant must specify the purity of the test material and for a non radiolabeled material a 98% purity is a minimum requirement.

Generally, the use of radiolabeled material of high purity is recommended to allow for complete accounting for all material balance as parent, degradates and volatiles.

The defficiencies listed as c and d, above, are less significant when the results turn out to indicate that degradation (hydrolysis) were not significant as it appears to be the case with 1,2-benzisothiazol-3(2H)-one. However, it is unclear whether any degradation that occured may have resulted due to microbial degradation and/or photodegradation since proper precautions were not taken in the experiment.

DATA EVALUATION RECORD

Hydrolysis Study of 1,2 Benzisothiazol-3(2H)-One (XBINX)

1.0 CONCLUSION

In aqueous buffer solutions, less than 10 percent of a 0.1 mg/mL solution of 1,2 Benzisothiazol-3(2H)-one (XBINX) was hydrolyzed. At the end of 30 days, the remaining XBINX at each pH ranged from 92.1 percent to 107.4 percent. These data suggest XBINX does not significantly degrade by hydrolysis at pH 5, 7, or 9. Most of the hydrolysis guideline requirements (Subdivision N, Section 161-1) were not fulfilled.

2.0 BACKGROUND

The test substance, 1,2 Benzisothiazol-3(2H)-one (XBINX), is to be used in indoor use pesticide formulations (proposed label was not attached). This study, conducted between May 22, 1996, and June 21, 1996, examined the hydrolysis of 1,2 Benzisothiazol-3(2H)-one (XBINX) under various controlled conditions. It was conducted in accordance with the U.S. EPA Pesticide Assessment Guidelines (Subdivision N, Section 161-1), but did not meet the requirements of the FIFRA Good Laboratory Practice Standards (see Statement in the Study Report).

3.0 METHODOLOGY

To each of three 100 mL volumetric flasks 10 mg of XBINX was added along with 1 mL of acetonitrile to aid in the dissolution of the XBINX. Each flask contained aqueous buffer solutions at pH 5, 7, or 9. Oxygen or air in the buffer solutions was removed by bubbling a stream of nitrogen gas for an hour, to prevent oxidation. Fifteen vials, used for each buffer solution, were filled, capped, and placed in a constant temperature bath pre-set at 30 ± 1°C. One of the fifteen vials at each pH was analyzed every four days (see comments below) over a thirty-day period for the remaining XBINX, and the expected oxidation products (BINX and saccharin). A separate study protocol was not provided.

3.1 Instrumentation and Apparatus

The solutions in the vials were analyzed by High Pressure Liquid Chromatography (HPLC) with UV detection (220 nm). Other apparatus used is described in an Appendix to this review.

3.2 Reagents and Materials

Water, methanol, and acetonitrile used for HPLC analysis were all HPLC grade. BINX, insoluble saccharin, and XBINX used as working standards were qualified standards according to the Study Report.

3.3 Procedure

Preparation of Working Standards

Standards were prepared by weighing 30 ± 5 mg of each saccharin, BINX, and XBINX standards into a 100 mL volumetric flask. Twenty mL of methanol was added to dissolve and dilute the standards. Working standards were then prepared by diluting the weighed standards with water (10:1).

Response Factor Determination

Ten µL of the above working standards were injected to determine the response factors of each component by dividing average HPLC peak areas by weight and dilution factors (10).

Sample Analysis

Ten µL samples were injected. If peaks indicating the presence of the above standards (suggesting presence of oxidation products) had been found, the samples were injected again, and areas for the two injections averaged. Oxidation product concentration would then have been calculated by multiplying the appropriate response factor by the average areas (expressed as mg/100 mL).

4.0 DATA SUMMARY

The investigator anticipated that XBINX breakdown products could be generated by one of two pathways; hydrolysis, and oxidation (see Appendix). The remaining XBINX at each pH ranged from 92.1 percent to 107.4 percent (see Table I and the attached chart). Less than 10 percent of hydrolysis was observed. New peaks were not observed suggesting no significant production of hydrolytic breakdown products. XBINX nor saccharin were detected in the samples suggesting the XBINX did not undergo oxidation.

5.0 QA/QC

QA/QC procedures were not documented.

6.0 COMMENTS

The itemized checklist below describes the major guidelines of Subdivision N, Section 161-1 for hydrolysis studies. Compliance and non-compliance of the study with the guidelines is noted.

- *The studies shall be conducted with each active ingredient in the product.* A proposed product label was not provided. It is not clear from the study report whether XBINX is the only active ingredient.

- *Where radioisotopic analytical techniques are used, studies shall be conducted with the analytical grade of each active ingredient in the product.* Radioisotopic

analytical techniques were not used in the study. Solvents used in the study, such as acetonitrile, water, and methanol, were all HPLC grade. The purity of the XBINX used for the hydrolysis procedure was not provided; it was only noted that the XBINX used as the working standard was "qualified standard."

- *Laboratory hydrolysis studied should be conducted in darkness.* This criterion was probably not met. It could not be determined from the study report if the study was conducted in darkness.

- *One or more concentrations of the test substance should be used and within the aqueous solubility range of the pesticide and at a level high enough to define the reaction kinetics and to purify and identify hydrolytic products.* This criterion was partially met. One concentration (0.1 mg/mL of XBINX) was used in the study. Acetonitrile was used to aid in the dissolution of XBINX. However, the solubility of the active ingredient was not provided. Kinetics were not determined because hydrolytic products were not identified.

- *For pesticides of low solubility, cosolvent may be added in the final solution without exceeding 1 percent by volume.* The criterion was met. Test substance in one mL of acetonitrile was diluted to 100 mL of aqueous buffer solution (one percent by volume).

- *The water used should be free of all live bacteria, and the glassware should be sterilized to minimize the possibility of microbial degradation of the test substance.* The criterion was probably not met. The study does not provide information on sterilization procedures or determinations.

- *Precautions should be taken during the test to minimize loss of test substance through volatilization.* Trapping system was not used in the study.

- *The temperature of the hydrolysis reaction should be maintained at 25 ± 1°C.* The criterion was not met as the temperature was maintained at 30 ± *1°C.*

- *Hydrolysis experiments should be carried out in solutions buffered at pH's of 5, 7, and 9.* The criterion was met.

- *Results of hydrolysis experiments using high concentrations of buffer should be carefully evaluated to determine whether buffer catalysis effects have occurred.* The type and concentration of the buffer solution was not clearly identified in the Study Report. However, potassium dihydrogen phosphate might have been used as the buffer (see p. 8 of the Study Report).

- *Aliquots should be taken at zero time and at sufficient sampling time intervals to define decline of the pesticide and appearance of products. The duration of the test need not exceed 30 days.* The criterion was met.

- *The method of adjusting pH.* No method for adjusting or monitoring pHs was explicitly discussed in the Study Report. It is possible that phosphoric acid was used.

- *Identification of each hydrolysis product produced in greater than 10 percent yield at any point during the course of the study, and material balance and half-life estimates for the parent substances.* Based on the HPLC results, no hydrolysis products were observed.

To summarize, most of the hydrolysis guideline requirements (Subdivision N, Section 161-1) were not fulfilled. Some other notes, not addressed above, are presented below:

- Samples were not taken "every four days" as noted in the procedures of the Study Report. The sampling intervals ranged from 2 to 7 days (see Table I).

- The HPLC results of the standards were not provided. Not all of the HPLC raw results were provided.

- The first three HPLC results were not clearly marked (see p. 10 to p. 15) and no peaks representing XBINX were observed. However, a peak at 7.28 minute of retention time was present (on p. 10; compared to the retention time of 8.14 or 8.16 for XBINX). What this peak represented was not clear.

- Information on year of manufacture and limit of detection for the HPLC instrumentation was not provided.